IN THE SPECIFICATION

Please amend the paragraph beginning at page 3, line 19, as follows:

This discovery is surprising notwithstanding the reported great success of RITUXAN® (rituximab) for the treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma. In particular, this discovery is surprising given the very high numbers of tumor cells observed in such patients and also given the fact that such malignant cells, e.g., CLL cells, typically do not express the CD20 antigen at the high densities which is characteristic of some B-cell lymphomas, such as relapsed and previously-treated low-grade non-Hodgkin's lymphomas. Consequently, it could not have been reasonably predicted that the CD20 antigen would constitute an appropriate target for therapeutic antibody therapy of such malignancies.

Please amend the paragraph beginning at page 6, line 5, as follows:

As noted, a particularly preferred chimeric anti-CD20 antibody is RITUXAN® (rituximab), which is a chimeric gamma 1 anti-human CD20 antibody. The complete amino acid and corresponding nucleic acid sequence for this antibody may be found in U.S. Patent 5,736,137, which is incorporated by reference in its entirety. This antibody, which is produced in a proprietary CHO cell expression system commercialized by IDEC Pharmaceuticals Corporation, is made by a CHO cell transfectoma which was deposited on November 4, 1992, under the provisions of the Budapest Treaty at the American Type Culture Collection, ~~located at 12301 Parklawn Drive, Rockville, MD 20852, now located at~~ 10801 University Boulevard, Manassas, Virginia 20110-2209 (ATCC 69119). This cell line was determined to be viable and will be replaced should it become non-viable during the term of deposit. This cell line was made irrevocably available upon issuance of the 5,736,137 patent and is available without restriction from the ATCC. This cell line will also be available without restriction during the lifetime of any patent that may issue based on this application.

Please amend the paragraph beginning at page 7, line 18, as follows:

Typically, treatment will be effected weekly, for about 2 to 10 weeks, more typically about 4 weeks. A particularly preferred dosage regimen will comprise administration of about ~~.375~~ 375 mg/kg weekly for a total of four infusions. Also, stepped-up dosing schedules may be even more preferable.

Please amend the paragraph beginning at page 8, line 1, as follows:

If radiation is used in conjunction with the therapeutic anti-CD20 antibody, it is preferred that an yttrium-labeled anti-CD20 antibody ~~we~~ be utilized, such as disclosed in U.S. Patent 5,736,137, incorporated by reference in its entirety herein. This antibody, 2B8-MX-DTPA, has reported efficacy in the treatment of B-cell lymphoma. The cell line that produces the 2B8 antibody has also been deposited at the American Type Culture Collection on June 22, 1993 under the provisions of the Budapest Treaty, and was made irrevocably available upon issuance of US Patent 5,736,137, without any restrictions. ~~Thus~~ This cell line was found to be viable and shall similarly be replaced during the lifetime of any patent that issues based on this application, should it become non-viable.

Please amend the paragraph beginning at page 9, line 1, as follows:

Two patients in whom we noted rapid reduction of blood tumor cells, which was associated with severe pulmonary infusion-related toxicity and thrombocytopenia, were studied. Also, two additional patients were collected from physician-submitted reports of adverse events related to RITUXAN® (rituximab) treatment. Pretreatment characterization of these patients included a median age of 60 years (range 26-73) with the diagnosis of B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), or transformed non-Hodgkin's lymphoma. All of these patients had elevated leukocyte counts as a consequence of blood tumor involvement, bulky adenopathy and organomegaly. All four patients developed unique syndrome of severe infusion-related reactions characterized by fever, rigors, bronchospasm with associated hypoxemia, requiring temporary cessation of RITUXAN® (rituximab) therapy. Concurrent with these symptoms, a rapid decrement in circulating tumor cell load (mean pretreatment 98 x 10^9 per L; range 73-132 vs. mean post-treatment 11 x 10^9 per L; range 3.7-24.6) with mild electrolyte evidence of rapid tumor lysis. Thrombocytopenia, a finding not commonly associated with RITUXAN® (rituximab) therapy was noted in all four patients (mean pretreatment 145 x 10^9 per L; range 57-277 vs. mean post-treatment 56 x 10^9/L; range 2-120), requiring transfusion in one case. Symptoms of this syndrome required hospitalization but resolved with supportive care. Subsequent RITUXAN® (rituximab) treatment were well tolerated in all patients. Two subsequent patients with CLL have been treated with high blood tumor counts utilizing stepped-up dosing (100 mg/m^2 day 1 followed by rest of therapy on day 2)

with demonstrated efficacy, thrombocytopenia but minimal infusion-related toxicity RITUXAN® (rituximab) administration in patients with hematologic malignancies who have blood tumor cell involvement may be associated with a higher frequency of severe initial infusion-related reactions and thrombocytopenia mandating careful clinical monitoring. Given the preliminary activity of RITUXAN® (rituximab) in these patients, future studies in CLL and PLL, utilizing a stepped-up dosing schedule, is to be conducted.

Please amend the paragraph beginning at page 10, line 10, as follows:

Unlabeled immunoglobulins (Mab) are attractive for the treatment of NHL as they may: mediate cytotoxicity with complement (CDC) or effector cells (ADCC); effect apoptosis; be less toxic, less immunogenic and possibly more effective than toxin- or drug-conjugated Mabs; not require the complex procedures needed for radiolabeled Mab therapy (RIT), and not produce the myelosuppression typical of high-dose RIT. Until recently, use of Mabs in the treatment of hematologic malignancies has been limited. However, the chimeric anti-CD20 Mab, RITUXAN® (rituximab), has a low toxicity profile and significant clinical efficacy and is now approved by the Food and Drug Administration (US FDA 11/97; EU 6/98) for the treatment of relapsed or refractory, low-grade or follicular (R=LG/F) NHL. In a single-agent clinical trial (PIII), of 166 patients with R-LG/F NHL treated with RITUXAN® (rituximab) at 375 mg/m^2 weekly for four infusions (study 102-05), the overall response rate (ORR) was 48% (6% CR and 42% PR). Median time to progression for responders was 13.1 months and duration of response 11.2 months. Median circulating B-lymphocyte counts dropped to zero following the first dose. CD3, CD4, CD8 and NK cell counts remained unchanged. B-cell recovery in peripheral blood began at 6-9 months and was complete by 9-12 months. No significant changes in serum complement levels were noted. The mechanism for action remains unresolved with CDC, ADCC, apoptosis and/or others being considered. In spite of the absence of a clinical/laboratory correlation, the contribution of CDC cannot be discounted. We have seen a correlation between higher absolute NK cell count at baseline and response to the Mab.

Please amend the paragraph beginning at page 11, line 12, as follows:

Note: N=166 patients from study 102-05, and 37 from 102-06. Abs. Count: NK, CD3=cells/mm3; ANC, Pts.=cells x ~~10e3/mm3~~ $10^3/mm^3$. P value for the difference between Abs. Counts.

Please amend the paragraph beginning at page 12, line 1, as follows:

ADCC may be an important mechanism for the clinical activity seen in patients treated with RITUXAN® (rituximab). Agents which enhance effector cell number and activity may synergize with the Mab. Studies of RITUXAN® (rituximab) in combination with cytokines, e.g., I1-2, G-CSF, GM-CSF, INF, are also ongoing.

Please amend the paragraph beginning at page 12, line 7, as follows:

Phase I/II Study of RITUXAN® (rituximab) in CLL

RITUXAN® (rituximab) is a monoclonal antibody targeting CD20 that has significant activity in the treatment of low-grade lymphoma (LGL). When given at a dosage of 375 mg/m^2 ~~weekly/four~~ weekly for four weeks the response rate in relapsed patients (PTS) was 43% (McLaughlin et al. (1998) J Clin Oncol 16(8):2825-33). Patients with small lymphocytic lymphoma had lower response rates (13%) than patients with other subtypes of LGL and lower serum levels of RITUXAN® (rituximab). Reduced response seen in SLL could be related to lower density of CD20 antigen and /or higher circulating B-cell counts. Both factors would be expected to impact (negatively) on response seen in CLL. In an attempt to maximize activities in CLL we are conducting a Phase I/II study. All patients receive a first dose of 375 mg/m^2 to minimize infusion-relapsed side effects. Subsequent weekly dosages (3) remain the same but are given at an increased dose level. Sixteen patients have been treated at dosages of 500-1500 mg/m^2. ~~Medium~~ Median age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. ~~Medium~~ Median white blood cell count was 40 x 10^9/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75 x 10^9/L (range, 16-160), median β_2 immunoglobulin was 4.5 mg/L (range, 3.1-9.2). Median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 mg/m^2); another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 mg/m^2 dose level has been fully evaluated. Eight patients have completed therapy (4 at 500 mg/m^2, 3 at 650 mg/m^2, 1 at 825 mg/m^2). One patient treated at 650 mg/m^2 achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.

Please amend the paragraph beginning at page 14, line 7, as follows:

Thus, by administering certain cytokines to CLL patients prior to or concurrently with administration of RITUXAN® (rituximab), the expression of CD20 on the surface of malignant B-cells may be upregulated, thereby rendering CD20, as well as other cell surface markers such as CD19, a more attractive target for immunotherapy.

Please amend the paragraph beginning at page 14, line 12, as follows:

A collaborative study has been initiated to a test for optimal cytokine doses for CD20 upregulation in vivo. The study protocol involves treating ten patients initially with GM-CSF at 250 mcg/m^2 SQ QD X 3, ten patients with IL-4 mcg/kg SQ QD X 3, and ten patients with G-CSF at 5 mcg/kg SQ QD X 3. Mononuclear cells will be separated by Ficon Hypaque centrifugation for apoptotic studies to determine if upregulation of CD20 translates to enhanced filling of tumor cells by RITUXAN® (rituximab).

Please amend the paragraph beginning at page 15, line 17, as follows:

Hence, anti-CD20 antibody therapy will be particularly useful for patients who are refractory or who have relapsed after treatment with chemotherapeutic drugs. RITUXAN® (rituximab) therapy may also be combined with radiotherapy in these patients. TBI with a low fraction size of 15 cGy to total doses of 75 to 150 cGy has been shown to be effective in about one-third of patients.

Please amend the paragraph beginning at page 16, line 3, as follows:

A Phase II trial is currently being conducted by CALGB in CLL patients. RITUXAN® (rituximab) and fludarabine are administered concurrently, followed by RITUXAN® (rituximab) consolidation versus fludarabine induction followed by RITUXAN® (rituximab). The goals of the study are (1) to determine in fludarabine treated CLL patients the complete response (CR) rate and toxicity profile of concurrent and consolidative RITUXAN® (rituximab) therapy (Arm I) and of consolidative RITUXAN® (rituximab) therapy (Arm II); (2) to assess the CR rate in patients receiving concurrent therapy with RITUXAN® (rituximab) and fludarabine (the inductive phase of Arm I); (3) to assess the frequency of conversion of a partial response (PR) to a CR or stable disease to ~~either~~ either PR or CR in CLL patients receiving consolidative therapy with RITUXAN® (rituximab); (4) to follow the effects of therapy with RITUXAN® (rituximab)

and fludarabine on the immunologic markers CD4, CD8, IgG, IgA and IgM; and (5) to examine progression-free survival and overall survival in Arms I and II.